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| EXAMINER | |
|---|---|
| HOUGHTLING, RICHARD A | |
| **ART UNIT** | **PAPER NUMBER** |
| 1609 | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/523,836 | BOULANGER ET AL. | |
| | Examiner | Art Unit | |
| | Richard A. Houghtling, Ph.D. | 1609 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *07 February 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *2-3 and 5-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,3 and 5-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 August 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07 February 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

*1.* Claims 2-3 and 5-11 are pending in the application received; receipt of a Preliminary Amendment also filed February 7, 2007 is acknowledged wherein claims 1 and 4 are cancelled. Applicants' preliminary amendment adding a paragraph to the specification corresponding to a cross reference to related applications is acknowledged and entered.

### *Foreign Priority*

2. Applicants' claim to foreign priority under 35 U.S.C. 119(a)-(d) is acknowledged; a certified copy was received from the International Bureau (PCT Rule 17.2(a)).

### *Information Disclosure Statement*

3. Acknowledgement of receipt of an information disclosure statement filed by applicants on February 7, 2007; examiner entered disclosures into the record and references considered.

### *Drawings*

4. The drawings are objected to because the EMSAs shown in Figure 2 lanes 1-8 cannot be visualized. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the

immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

***Claim Rejections - 35 USC § 112***

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-3 and 5-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The factors considered in the Written Description requirement are (1) *level of skill and knowledge in the art,* (2) *partial structure,* (3) *physical and/or chemical properties,* (4) *functional characteristics alone or coupled with a known or disclosed correlation between structure and function*, and the (5) *method of making the claimed invention.*

While all of the factors have been considered, only those required for a *prima facie* case are set forth below:

The specification discloses a method for the treatment of mastitis *in vitro* but not for *in vivo* administration.

The claims are drawn to methods of treatment for mastitis comprising administration of a specific NF-κB inhibitor to a subject in need thereof *in vivo.*

Vas-Cath Inc. V. Mahurka, 19 USPQ2d 1111, states that applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of claim 5 indicates that these claims are drawn to a genus, i.e., any drug that is a specific NF-κB inhibitor; yet the specification does not teach which NF-κB inhibitors are specific for *in vivo* treatment of mastitis in a subject in need thereof.

The disclosure of a single disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus. The present claim encompasses any and all drugs that can exist which are specific NF-κB inhibitors. There is substantial variability among the species of drugs encompassed within the scope of the claims corresponding to specific NF-κB inhibitors because these

drugs represent an entire class of molecules that can have widely differing structures and corresponding biological activities. Further, defining the drug in functional terms would not suffice in the absence of a disclosure of structural features or elements of the drug that would have the stated function. Applicant is describing what the drug does rather than what it is.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Consequently, the Examiner notes that the claimed invention which is drawn to a sub-genus of drugs may be adequately described if there is a (1) sufficient description of a representative number of species, or (2) by disclosure of relevant, identifying characteristics sufficient to describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention. Here, the specification discloses only that the genus of NF-κB inhibitors may be further sub-divided into specific and non-specific inhibitors. Since the claimed sub-genus encompasses drugs yet to be discovered, the disclosed requirement that a specific NF-κB inhibitors be employed does not satisfy the requirement that a representative and substantial portion of the claimed sub-genus be disclosed.

Weighing all the factors, the breadth of the claims reading on drugs yet to be discovered, the lack of correlation between structure and function of the drugs, level of

knowledge and skill in the art, one of ordinary skill in the art would not recognize from the disclosure that the applicant was in possession of NF-κB inhibitors which work *in vivo*. At best, the disclosure simply indicates that one should run tests on a wide spectrum of compounds in the hope that at least one of them will work. Neither the exemplary embodiments nor the general method of the specification appear to describe structural features, in structural terms, that is common to the inhibitors. That is, the specification provides neither a representative number of drugs to describe the claimed inhibitors, nor does it provide a description of structural features that are common to the drugs. In essence, the specification simply directs those skilled in the art to go figure out for his or herself the structure of the claimed drug and then determine if it has *in vivo* activity.

The written description requirement is not satisfied.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-3, 5-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for *in vitro* treatment of cells isolated from a cow suffering from mastitis comprising administration of a NF-κB inhibitor, does not reasonably provide enablement for *in vivo* administration of the NF-κB inhibitor. The specification does not enable any person skilled in the art to which it pertains, or with

which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The language of the claims is not limited to *in vitro* treatments and encompasses treating subjects (defined in the specification to include warm-blooded animal species such as e.g. ruminants such as cattle, sheep, goats, buffalo etc. (col. 1, ¶ 19) *in vivo* and as such does not have support in the specification. There is insufficient disclosure to reasonably predict that the methods and compositions of the instant specification would inhibit NF-κB *in vivo*. This is merely an unsubstantiated assertion with no evidence to support the contention that the *in vitro* studies of the specification are indicative of *in vivo* activity. Applicant has only shown EMSA data from cultured milk cells treated with NF- κB inhibitors *in vitro*, not treating warm-blooded animals with the NF- κB inhibitors or shown an art recognized correlation between the data shown and the scope of the claimed invention. The artisan would recognize and appreciate that there is no known correlation between *in vitro* and *in vivo* results, because the artisan recognizes that an *in vitro* assay cannot duplicate the complex conditions of *in vivo* therapy. In the *in vitro* assay, the NF- κB inhibitor is present during the entire exposure period. This is not the case *in vivo* where target site exposure may be delayed or i-nadequate. In addition, variables such as biological stability, half-life, or clearance from the blood are important parameters in achieving successful therapy. The composition may be inactivated *in vivo* before producing a sufficient effect. In addition, the composition may not reach the target cells because of its inability to penetrate tissues or

cells where its activity is to be exerted, may be absorbed by fluids, cells, and tissues where the composition has no effect and/or a large enough local concentration may not be established. There are no specific teachings in the disclosure that would allow one to have a reasonable expectation of success in transferring the *in vitro* method to treat warm-blooded animals suffering from acute or chronic mastitis. One is only left with speculation and an invitation to experiment. Therefore, the claimed invention lacks an enabling disclosure.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "specific inhibitor" in claim 5 is a relative term which renders the claim indefinite. The term "specific inhibitor" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Within the specification, applicants' state, "The NF-κB inhibitors for use in the treatment of mastitis can be specific inhibitors of NF-κB or can be non-specific," (col. 1, ¶ 16), but applicants' fail to define the term "specific inhibitors." Using a definition found

in a textbook entitled, Pharmacology by Rang et al. (1995), drug specificity is determined by the ability of a drug to show a high degree of binding-site selectivity as well as ligand specificity of the drug target thereby recognizing a ligand which is of a certain precise type and that ignore other closely related molecules (p. 6, 1st ¶, lines 4-11). Hence, drug specificity is a relative term, as no drug acts at solely at its target (p. 6, 3rd ¶, lines 40-41). Applicants' do provide many examples of known NF- κB inhibitors (col.1, ¶ 6-14), however applicants' do not provide any insight as to which inhibitor(s) listed is/are specific or non-specific for the treatment of mastitis.

***Claim Rejections - 35 USC § 103***

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 2-3 and 5-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nickerson et al. (1986) further in view of Tegeder et al. (2001) or Bauer et al. (1989) and Pahl et al. (2001).

Independent claims 8 and 9 are each drawn to a method of treatment for mastitis comprising administering to a subject in need thereof an effective amount of NF-kB inhibitor or NF-kB inhibitor and antibiotic, respectively. The NF-kB inhibitor used in the method of claim 8 is further limited to those selected from 15d-PGJ2, tepoxalin, cycloepoxydon, (+)cycloepoxydon, (-)cycloepoxydon, sodium diethyldithiocarbamate, gliotoxin, MG-132, BAY 11-7082, BAY 11-7085 or bortezomib (claim 6). Additional limitations to the method of claim 8 include: treatment of acute mastitis (claim 3), use of a specific NF-kB inhibitor (claim 5) and intramammary administration (claim 7). The method of treating acute mastitis is also further limited by claim 11 which specifies several NF-kB inhibitors to be selected from 15d-PGJ2, tepoxalin, cycloepoxydon,

(+)cycloepoxydon, (-)cycloepoxydon, sodium diethyldithiocarbamate, gliotoxin, MG-132, BAY 11-7082, BAY 11-7085 or bortezomib.

In addition to treatment of acute mastitis, the method of claim 8 is also further limited by claim 2 to include chronic mastitis using an NF-kB inhibitor selected from 15d-PGJ2, tepoxalin, cycloepoxydon, (+)cycloepoxydon, (-)cycloepoxydon, sodium diethyldithiocarbamate, gliotoxin, MG-132, BAY 11-7082, BAY 11-7085 or bortezomib (claim 10).

Nickerson et al. teaches treatment of acute bovine mastitis by intramammary administration of anti-inflammatory agents with or without antibiotics. Acute mastitis induced experimentally results in a measurable loss of milk yield. Treatment of cows with ibuprofen resulted in the most rapid recovery of milk yield compared with methylprednisolone or flumethasone treatments (p. 1740 lines 4-22). Another study examined acute mastitis treated with an intramammary product containing amoxicillin (antibiotic) and beclomethasone (steroidal anti-inflammatory); reductions in rectal temperatures, leukopenia, and rise in milk pH were observed (p. 1740, lines 30-42). Nickerson et al. also teaches that *in vitro* treatment of polymorphonuclear leukocytes (PMNL), the primary cell contributing to increased somatic cell counts in the milk of cows suffering from mastitis, using methylprednisolone reduced PMNL degranulation and release of lactate dehydrogenase (p. 1740, lines 29-34). Taken together, Nickerson et al. concludes that intramammary treatment of mastitis using anti-inflammatory agents such as ibuprofen and methylprednisolone may give both sought after benefits of more rapid milk yield recovery and less mammary inflammation.

Nickerson et al. does not teach that the anti-inflammatory agents used methylprednisolone (a glucocorticoid) or ibuprofen (nonsteroidal anti-inflammatory agent) is effective NF-kB inhibitors.

Tegeder et al. teaches anti-inflammatory agents belonging to the "cyclooxygenase inhibitors" class of drugs that also have pharmacological effects on transcriptional factors, kinases, cell cycle proteins, heat shock proteins or nuclear receptors. Of particular interest is Table I (p. 2059) which outlines several different anti-inflammatory agents, relative inhibitory concentrations ($IC_{50}$ values) necessary to inhibit cyclooxygenases 1 and 2, as well as other proteins which include transcription factors (NF-kB, AP-1, cMyc and STAT) as well as several kinases IKK, MAP kinases, etc. The data presented in Table I shows that several "cyclooxygenase inhibitors" are also effective inhibitors of NF-kB activation, including R-flurbiprofen S-flurbiprofen, aspirin, sodium salicylate, and ibuprofen. Although not listed in Table I, Tegeder et al. mentions that dexamethasone (a glucocorticoid) is well known to inhibit NF-kB activation (p. 2058, col. 1, lines 48-53) and that flurbiprofen may share a similar mechanism of action (p. 2061, col. 2, lines 20-44). Thus, Tegeder et al. teaches that glucocorticoid steroids, such as dexamethasone or methylprednisolone, as well as, nonsteroidal anti-inflammatory agents such as ibuprofen, flurbiprofen, aspirin and sodium salicylate also act as NF-kB inhibitors, but does not teach methods of using such agents for treatment of mastitis.

Taken together, the teachings of Nickerson et al. demonstrate that the anti-inflammatory agents, ibuprofen and methylprednisolone, each known to inhibit

activation of NF-kB, further provide beneficial effects to reduce inflammation and produce a more rapid recovery of milk yield. Because ibuprofen is listed within Table I and it is shown that it inhibits NF-kB activation (Tegeder et al.), it is *prima facie* obvious to one of ordinary skill in the art to combine these two teachings resulting in applicants method of treatment for mastitis comprising use of NF-kB inhibitors (claim 8). Tegeder et al. teaches that the NF-kB inhibitory effects of the cyclooxygenase inhibitors are relative yet somewhat distinct. Thus, it would have been obvious to one of ordinary skill in the art to use judicious selection and routine optimization, well within the purview of the skilled artisan, to seek to use the most specific NF-kB inhibitor (claim 5) available as well as for treatment of acute (claim 3) or chronic (claim 2) mastitis. Flurbiprofen and ibuprofen inhibit NF-kB activation over concentration ranges of 10 μM to 1 mM whereas aspirin (2-10 mM) and sodium salicylate (5-20 mM) require much greater concentrations, indicating the latter to be less NF-kB specific.

Finally, it would have been obvious to one of ordinary skill in the art to apply the teachings of Nickerson et al..regarding the beneficial effects that result from the combination of beclomethasone and amoxicillin (p. 1740, lines 36-50) and instead substitute a NF-kB inhibitor to replace beclomethasone (glucocorticoid and hence inhibitor of NF-kB activation) to treat mastitis (claim 9).

10. Claims 2-3 and 5-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bauer et al. (1989) and Onoda et al. (2000, found in applicants' IDS) further in view of Pahl et al. (1996).

Independent claims 8 and 9 are each drawn to a method for the treatment of mastitis comprising administration to a subject in need thereof an effective amount of a NF-κB inhibitor (claim 8) or a NF-κB inhibitor and an antibiotic (claim 9). Claims 2 and 3 each depend from claim 8, each of which further limits the method of treatment to cases involving chronic or acute mastitis, respectively. Claims 10 and 11 depend from claims 2 and 3 respectively and claim 6 further limits the method of claim 8, each of which further limits the method of treatment one NF-κB inhibitor selected from 15d-PGJ2, tepoxalin, cycloepoxydon, (+)cycloepoxydon, (-)cycloepoxydon, sodium diethyldithiocarbamate, gliotoxin, MG-132, BAY11-7082, BAY11-7085 or bortezomib. The method of claim 8 is further limited by dependent claims 5 or 7, each of which is directed to the NF-κB inhibitor that is a specific inhibitor (claim 5) or by its route of intramammary administration (claim 7).

Bauer et al. (1989) describes the isolation of gliotoxin, a fungal metabolite with cytotoxic and immunosuppressive properties isolated from a bovine udder infected by *Aspergillus fumigatus* (see p. 45, Abstract and 3rd ¶, lines 1-3). As discussed in Bauer et al., *in situ* production of gliotoxin by *A. fumigatus* results in the initiation of a chronic state of immunological unresponsiveness characterized by inhibition of macrophage phagocytosis and the abrogation of T-cell-mediated immune mechanisms (p. 50, lines 1-4). Thus, Bauer et al. teaches that gliotoxin possesses immunosuppressive properties necessary for use in the treatment of mastitis, but does not directly teach of gliotoxin as a NF-κB inhibitor.

As described above for Onoda et al., curcumin is known to have diverse chemical, biological and pharmacological properties including an anti-inflammatory function mediated by its ability to inhibit NF-κB activation and reduce bacterial-induced acute mastitis but it does not specifically teach the group of NF-κB inhibitors listed in Claim 11. Though curcumin is a NF-κB inhibitor and effective in reducing acute mastitis, Onoda et al. does not teach any of the NF-kB inhibitors for chronic inflammation due to mastitis.

Finally, Pahl et al. (1996) is relied upon to show that gliotoxin specifically inhibits NF-κB activity in leukocytes without affecting the DNA-binding activity of other transcription factors thereby indicating that gliotoxin is a specific NF- κB inhibitor (p. 1833, col. 1, lines 8-15 and 24-27; col. 2, lines 1-4; and Figure 1). Pahl et al. does not however utilize the gliotoxin for treatment of mastitis.

Specifically, the instant method of claim 8 is drawn for the treatment of mastitis using a specific NF- κB inhibitor (claim 5) or for treatment of acute mastitis (claim 3) using one NF-κB inhibitor selected from 15d-PGJ2, tepoxalin, cycloepoxydon, (+)cycloepoxydon, (-)cycloepoxydon, sodium diethyldithiocarbamate, gliotoxin, MG-132, BAY11-7082, BAY11-7085 or bortezomib (claim 11).

The rationale to combine the findings of Bauer et al. (1989), Onoda et al. (2000) and Pahl et al. (1996) shall follow. Pahl et al. (1996) is relied upon solely as evidence that gliotoxin has specific NF-κB inhibitory effects in immune cells, thereby providing a mechanism and validating the findings by Bauer et al. (1989). Taken together, these two studies provide impetus to further examine the role of NF-κB in the intramammary

inflammatory response. In doing so, Onoda et al. (2000) demonstrated that inhibition of NF-κB by curcumin (a structurally unrelated compound) an intramammary inflammatory mediator, nitric oxide, was reduced in organ cultures stimulated by LPS, an art recognized stimulus for a bacterial infection, and co-incubated with the NF-κB inhibitor curcumin. Therefore it would have been *prima facie* obvious to one of ordinary skill in the art to combine these teachings with the result being the method of the claimed invention for the purpose of dampening or preventing activation of immune cells in response to mastitis to minimize damage to the intramammary epithelia cells. Furthermore, it would have been obvious at the time of the invention to also include an antibiotic since bacterial infection is a common cause of mastitis in warm-blooded animals. Finally because both curcumin and gliotoxin inhibit NF-κB activation and gliotoxin is a known specific inhibitor (claim 5) of NF-κB, it would have been obvious to one of ordinary skill in the art to substitute gliotoxin for curcumin in a treatment method pertaining to an acute case of mastitis (claims 3 and 8).

## Conclusion

In conclusion, no claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard A. Houghtling, Ph.D. whose telephone number is 571-272-9334. The examiner can normally be reached Monday to Thursday from 8:00 am - 5:00 pm. The examiner can also be reached on alternate Fridays.

The Group 1600 fax phone number where this application or proceeding is assigned is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center representative whose telephone number is (571)-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker, can be reached on 571-272-0911.

Richard A. Houghtling, Ph.D.

JEFFREY STUCKER
SUPERVISORY PATENT EXAMINER